

Association of serum pentraxin 3 levels with co-morbidities in acute ischemic stroke patients

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ABSTRACT

Aims: Pentraxin 3 (PTX3), an indicator of the inflammatory process, is an acute-phase protein (AP) with biphasic effect. In the present study, the relationship between PTX3 levels and stroke risk factors in stroke patients were analyzed.

Methods: Acute stroke patients (n=56) were diagnosed using imaging techniques and clinical examination along with their laboratory results. The control group consisted of thirty healthy individuals. Blood samples of the patient group were obtained within the first 24 hours of stroke onset. Serum pentraxin levels of both groups were analyzed and their relationship with stroke risk factors evaluated.

Results: A total of 86 people, 56 stroke patients and 30 healthy controls were included in the present study. Out of the participants, in both groups, 50% were female (p=1.000). No significant difference was determined between the groups in terms of age (p=0.226). The pentraxin value in the patient group was significantly lower than that in the control group (p=0.003). No significant difference between gender and presence of comorbidities in terms of PTX3 value (p>0.05) were present. Likewise, no significant correlation could be established between PTX3 value and National Institutes of Health Stroke Scale (NIHSS) and age in the patient group.

Conclusion: Serum PTX3 can be used as a biomarker in acute stroke patients. However, it cannot be used as a predictor in determining prognosis during the acute period.

Keywords: Stroke, pentraxin 3, NIHSS, comorbidity

INTRODUCTION

Stroke, either hemorrhagic or ischemic, is associated with high mortality and morbidity rates and is the second top cause of morbidity.¹ The Cui² study reported 7.3 million ischemic strokes in 2019. Associated financial burden spike up according to emerging motor deficits, re-hospitalization times, neurotic disorders such as anxiety and depression, loss of workforce, and stroke relevant psychocological, intellectual, functional and socio-professional problems.³ Therefore, early diagnosis and treatment along a cost-effective disease management are of critical importance.

Various biomarker studies have been conducted for early stroke diagnosis and treatment. Soluble TNF- α receptor concentration was found to be high in recurrent vascular incidents and subsequent seizures.⁴ IL-1 β was found to have high plasma concentrations in stroke patients with clinical deterioration.⁵ There are meta-analyses showing that Leptin with an anti-apoptotic activity, is detected at high levels as a risk biomarker in stroke patients.⁶ An experimental study determined a significant association between low adiponectin levels and increased ischemic stroke mortality⁷ mediated by NADPH oxidase inhibition and endothelial nitric oxide (NO)

synthase phosphorylation.⁸ A further study has established it as a potential biomarker for ischemic stroke along with other risk factors.⁹ Interleukin-6 (IL-6)¹⁰ and IL-10¹¹ plasma levels have been found to be significantly correlated with stroke size.

In the pathophysiology of stroke, inflammation increases ischemic injury and plays a role in recovery. Ischemia driven oxygen and glucose deficiency leads to disruption of the ionic gradient. The amount of intracellular calcium increases due to glutamate released from these depolarized neurons and apoptosis, activating necrotic and auto phagocytosis pathways. Intracellular calcium increase leads to mitochondrial dysfunction and activation of proteases, free radicals, and phospholipases. Calcium accumulated in the mitochondria causes the opening of the mitochondrial permeability transition pore (mtPTP) and the release of cytochrome c. As a result, cellular apoptosis occurs due to mitochondrial collapse. The intracellular entry of calcium, nitric oxide synthase (NOS) activation, NO production and free radical formation and inflammation caused by ischemia lead to the release of inducible NOS (iNOS) from neutrophils. Free radicals regulate the PI3-kinase/act pathway

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and κ NF- κ B transcription factor up. The triggering of P2X7 receptors in oligodendrocytes results with calcium increase and mitochondrial depolarization. There is also an increase in C-reactive protein level due to inflammation in stroke. Pentraxin 3 (PTX3) from the pentraxin family is also an acute-phase protein (APP).¹² Pentraxin 3, consisting of 381 amino acids, is secreted rapidly depending on the soluble receptor recognition pattern. PTX3 is considered to have a protective effect in inflammation.¹³ Hence, there are studies proposing it as a biomarker in cerebral and cardiovascular diseases.¹⁴ In the present study, the relationship of PTX3 blood levels of acute stroke patients with chronic diseases and its potential as a biomarker is investigated.

METHODS

This study was approved by Erzincan Binali Yıldırım University Clinical Researches Ethics Committee (Date: 02.03.2023, Decision No: 2023-05/2). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Neurological examinations were performed and magnetic resonance images were obtained from all patients admitted to the stroke clinic of our hospital. Ischemic stroke was diagnosed using National Institute of Health Stroke Scale (NIHSS) and potential risk factors (diabetes, chronic renal failure, carotid stenosis, atrial fibrillation, congestive heart failure) were recorded. Routine blood samples were collected from patients within the first 24 hours of stroke onset. In the control group participants, blood samples were obtained according to convenience sampling method. Exclusion criteria were less than 18 years of age, presence of a systemic or chronic inflammatory disease history, antibiotic and non-steroidal anti-inflammatory therapy enrollment for the last 2 weeks, and recurrent stroke presence. In the age and gender matched control group, exclusion criteria were presence of lung, neurodegenerative, coronary artery disease history, and atrial fibrillation presence. Blood samples obtained from all participants of the present study were centrifuged at 3000 rpm for 10 minutes. The plasma portion was placed in Eppendorf tubes and stored at -80°C . After the samples were obtained, the blood samples were kept at 20°C overnight to ensure slow thawing. The next day, it was kept at $+4^{\circ}\text{C}$ and then brought to room temperature to enable complete thawing. PTX3 levels were measured using the commercially available enzyme-linked immunosorbent assay, QuantiGlo (R&D System Inc., Minneapolis, Minnesota, USA). MRI studies were performed with Siemens® Magnetom area 1.5-T and GE-HD 3-T MR devices with echo planar imaging system. Imaging protocol was defined with DWI weighted images. The parameters used for imaging were: TR/TE=9000/84 ms for 1.5 T MR examination; field of view (FOV)=230 mm; section thickness=4.0 mm; cross-sectional gap=1.5 mm. 3 for MRI MR/TE=6000/80 ms; field of view (FOV)=240 mm; section thickness=4.0 mm. In order to calculate infarct volume, Cavalieri method based on the diffusion weighted compared magnetic resonance images. In order to perform calculations with this method, special Stereo Investigator software and

an image analysis system equipped with a point grid area measurement scale were employed.

Statistical Analysis

SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) 22 software was employed to analyze the data obtained in the present study. Descriptive data were presented as n, percentage values for categorical data, and median interquartile range (25-75 percentile values) for continuous data. Chi-square analysis (Pearson Chi-square) was used to compare categorical variables between groups. Compliance of continuous variables with normal distribution was evaluated using Kolmogorov-Smirnov test. Mann-Whitney U test was used for the comparison of paired groups. Spearman correlation test was used to analyze the relationship between continuous variables. Receiver operating characteristic (ROC) curves were drawn to measure the diagnostic value of venous PTX3 values. $p < 0.05$ is the threshold level for statistical significance level in the present study.

RESULTS

A total of 86 participants, 56 (65.1%) stroke patients and 30 (34.9%) controls, have participated in the study. 28 (50%) of those were male and 28 (50%) were female in the patient group and 15 (50%) of those were male and 15 (50%) were female in the control group. There was no significant difference between the groups in terms of age ($p=0.226$). The pentraxin value in the patient group is significantly lower compared to the control group ($p=0.003$) (Table 1).

Table 1. Comparison of group characteristics

	Patient (n=56)	Control (n=30)	
	n (%)	n (%)	p*
Gender (male, female)	28 (50.0)/28 (50.0)	15 (50.0)/15 (50.0)	1.000
	Median (IQR)	Median (IQR)	p**
Age	72.0 (61.0-79.0)	68.0 (65.0-76.0)	0.226
PTX3 (ng/ml)	2.8 (2.2-5.1)	5.0 (3.2-9.7)	0.003

*Square analysis, **Mann-Whitney U test, IQR: Interquartile range, PTX3: Pentraxin 3

The ability of venous PTX3 to predict acute ischemic stroke was investigated using ROC analysis and thus the cut-off value was determined. When 3.32 is taken as cut-off value for venous PTX3, a sensitivity of 69.6% and a specificity of 73.3% was determined indicating as PTX3 as a potential predictor (Figure 1).

Out of the stroke patients included in the study, 67.9% had hypertension (HT), 30.4% had atrial fibrillation (AF), 30.4% had coronary artery disease (CAD), 25% had hyperlipidemia (HL), and 21.4% had congestive heart failure (CHF), 19.6% had diabetes mellitus (DM), 19.6% had chronic renal failure (CRF) and 10.7% had a history of ischemic cerebrovascular disease (ICD) (Figure 2).

No significant difference was observed between gender ($p=0.781$), presence of DM ($p=0.773$), HT ($p=0.261$), CRF ($p=0.257$), AF ($p=0.624$), CAD ($p=0.527$), previous stroke

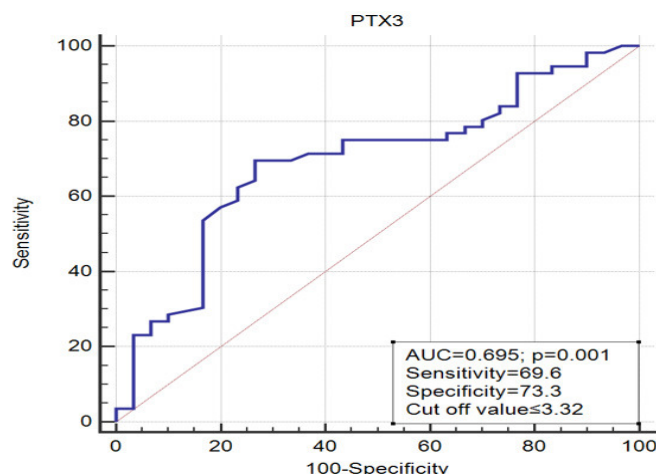


Figure 1. ROC curve of venous PTX3 value for acute ischemic stroke
ROC: Receiver operating characteristic PTX3: Pentraxin 3

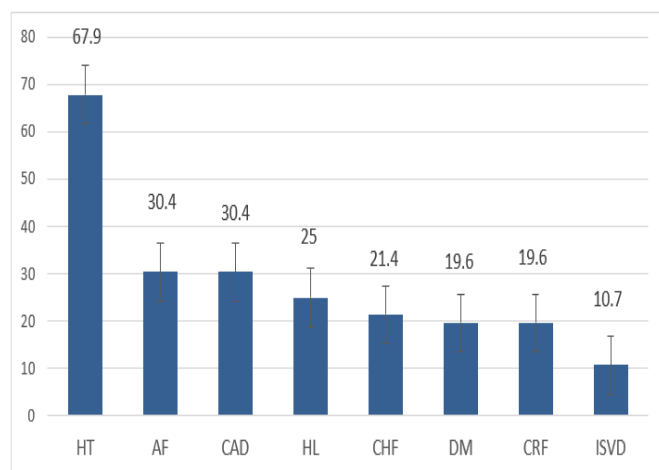


Figure 2. Stroke patients' co-morbidities

HT: Hypertension, AF: Atrial fibrillation, CAD: Coronary artery disease, HL: Hyperlipidemia, CHF: Congestive heart failure, DM: Diabetes mellitus, CRF: Chronic renal failure

($p=0.093$), HL ($p=0.820$), and presence of CHF ($p=0.448$) in terms of PTX3 value (**Table 2**).

No significant correlation was observed in the patient group in terms of PTX3 value, NIHSS, and age ($p=0.478$; $p=0.704$) respectively). There was no significant correlation between NIHSS value and age ($r=0.027$; $p=0.843$).

DISCUSSION

Stroke is a disease with a complex pathophysiology. Whereas activated pathways increase brain injury in the acute period, they also play a role in neurogenesis and angiogenesis in the chronic period. Several studies have shown that some plasma soluble factors have not only positive impacts, but also negative ones on the neurovascular unit (NVU).^{15,16} VEGF, for instance, acts by disrupting the blood brain barrier (BBB) in acute ischemia. It also has a significant role in the recovery of brain tissue because it provides angiogenesis in the chronic period.¹⁷ Similarly, MMP-9 damages NVU dysfunction in the acute period¹⁸ and plays a role in neurogenesis and angiogenesis in the chronic period.¹⁹ PTX3 also has a biphasic effect. Akihiro Shindo et al.²⁰ showed that GFAP-positive astrocytes are the major source of PTX3 in white matter strokes. Another study by Shindo et al.²¹, in a rat model of focal

Table 2. Comparison of stroke patients' PTX3 values between gender and comorbidity variables

		PTX3 (ng/ml)	P*
		Median (IQR)	
Gender	Male	2.7 (2.3-3.8)	0.781
	Female	2.9 (1.8-6.1)	
DM	+	2.7 (1.7-4.4)	0.773
	-	2.8 (2.4-5.7)	
HT	+	2.8 (2.0-3.8)	0.261
	-	2.9 (2.6-8.8)	
CRF	+	2.6 (1.9-3.2)	0.257
	-	2.9 (2.3-7.6)	
AF	+	2.9 (2.6-5.7)	0.624
	-	2.8 (2.0-4.4)	
CAD	+	2.9 (2.5-5.7)	0.527
	-	2.8 (2.0-4.4)	
ISVD	+	7.4 (3.2-26.5)	0.093
	-	2.8 (2.2-4.3)	
HL	+	2.8 (2.0-3.2)	0.820
	-	2.8 (2.3-5.7)	
CHF	+	2.7 (1.5-8.3)	0.448
	-	2.9 (2.3-5.1)	

*Mann Whitney U test was applied. PTX3: Pentraxin 3, IQR: Interquartile range, DM: Diabetes mellitus, HT: Hypertension, CRF: Chronic renal failure, AF: Atrial fibrillation, CAD: Coronary artery disease, HL: Hyperlipidemia, CHF: Congestive heart failure

grey matter ischemic stroke, reported that the major source of PTX3 was GFAP-positive astrocytes. PTX3 binds and inhibits VEGF which damages the BBB. Thus, it diminishes the impact of the potential injury. However, studies on the effect of PTX3 on tight junction proteins (such as ZO-1, claudins and occludins) are needed to determine the effectiveness of PTX3 on the BBB. Brain recovery requires coordination in neurogenesis and angiogenesis processes.²² One study showed that downregulation of PTX3 promotes compensatory angiogenesis, while another study²⁰ reported that PTX3 in mice exhibited less angiogenesis after stroke.²³ Since cerebral white matter is mainly composed of axonal bundles surrounded by a myelin sheath, the process of differentiation-proliferation of oligodendrocyte precursor cells is very important in the development of effective treatments for white matter stroke.

In a study, it was found that PTX3 plasma levels were higher in acute cerebral ischemia patients compared to the control group. In the same study, it was found that elevated PTX3 level was correlated with elevated NIHSS and inversely correlated with HDL level.¹⁴

The present study determined that, PTX3 level, as a potential predictor, was significantly lower in the patient group than in the control group with 69.6% sensitivity and 73.3% specificity ($p=0.003$). The difference between the studies was thought to be due to genetic polymorphism.²⁴

In a study on acute myocardial infarction, PTX3 was found to have a higher prognostic value compared to CRP, troponin T and creatine kinase.²⁵ Ahriçulesei et al.²⁶ found that PTX3, CRP, TNF- α , and IL-6 levels were higher in type 2 diabetic

patients compared to prediabetic patients. Soeki et al.²⁷ found that PTX3 levels were higher in blood from the left atrial appendage compared to blood from the peripheral artery in atrial fibrillation. In an experimental study, PTX3 was shown to lower blood pressure and improve inflammation and cardiomyocyte apoptosis in rats.²⁸ In a study conducted in patients with chronic kidney disease (CKD), serum PTX3 levels were found to be high.²⁹ In a study of patients with heart failure (HF) and normal ejection fraction, elevated basal circulating levels of PTX3 have been shown to be associated with increased cardiovascular mortality or worsening of HF (70).³⁰ In a study by Yi et al.³¹ on the severity of carotid artery stenosis, PTX3 and LDL-C levels were correlated. However, Lee et al.³² showed that PTX3 and HDL-C levels were positively correlated. In the present study, no significant differences in PTX3 levels across both sexes and the presence of comorbidities (diabetes mellitus, atrial fibrillation, hypertension, chronic renal failure, congestive HF, coronary artery disease, hyperlipidemia) were determined ($p>0.05$).

PTX3, which promotes long-term recovery of cerebral blood flow, angiogenesis and neuronal viability after cerebral ischemia, is among the therapeutic targets.³³ There are studies showing that PTX3 is an indicator of mortality and poor prognosis after ischemic stroke.^{34,35}

There was no significant relationship between neurological recovery and long-term prognosis in ischemic stroke patients treated with thrombolytic therapy.³⁶ Zhang et al.³⁷ found that serum PTX3 level was elevated in patients with acute minor stroke due to large arterial atherosclerosis and was an indicator of unfavorable outcome together with LDL cholesterol. In the present study, there was no significant correlation between PTX3 and NIHSS ($p>0.05$, $p=0.478$). A further study determined that PTX3 level did not change according to gender and increased proportionally with age in stroke patients,³⁴ whereas no significant difference was determined in terms of gender and age in another study.³⁸ In the present study, no statistically significant difference was found between PTX3 and gender and age (respectively, $p=0.781$, $p=0.704$).

Limitations

The limitations of the present study are as follows; Limited number of participants in both patients and control group, disregard of other inflammatory parameters, lack of cell culture studies, lack of genetic polymorphism analyses.

CONCLUSION

As a result, this study on PTX3 level in acute ischemic stroke patients revealed that PTX3 level may be a potential diagnostic biomarker. The present study has shown that pentraxin value in the patient group is significantly lower compared to the control group ($p=0.003$). The review of the relevant literature presented differing results in many of the studies related with serum PTX3 level. Only few of the studies in the review of the relevant literature, presented PTX3 level in acute ischemic stroke patients whose blood samples were collected at differing times (in the present study blood samples were taken within the first 24 hours after stroke onset unlike other studies in which the samples were taken within the first 48

hours). Other studies on PTX3 were experimental studies. Unlike these studies in which PTX3 levels were found to be elevated, in the present study serum PTX3 levels were low. The underlying reasons for the different results obtained could be due to differences in methodology and polymorphism. In addition, unlike other studies, this study suggests that PTX3 level is a potential diagnostic marker, not a prognostic one. However, studies with larger patient groups accompanied by pathophysiological investigations are required to verify the findings of the present study.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by Erzincan Binali Yıldırım University Clinical Researches Ethics Committee (Date: 02.03.2023, Decision No: 2023-05/2).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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